# HOLLAND & KNIGHT LLP

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Suite 2000
Atlanta, Georgia 30309-3400

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404-881-0470 Fax
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**MESSAGE:**

| | | | |
|---|---|---|---|
| Appellants: | Linda G. Cima, Edward W. Merrill, and Philip R. Kuhl | | |
| Serial No.: | 08/398,555 | Art Unit: | 1654 |
| Filed: | March 3, 1995 | Examiner: | Jeffrey E. Russel |
| For: | *CELL GROWTH SUBSTRATES WITH TETHERED CELL GROWTH EFFECTOR MOLECULES* | | |

# 1617926_v1

PTO/SB/21 (08-03)
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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

Total Number of Pages in This Submission

| | |
|---|---|
| Application Number | 08/398,555 |
| Filing Date | March 3, 1995 |
| First Named Inventor | Linda G. Cima, et al. |
| Art Unit | 1654 |
| Examiner Name | Jeffrey E. Russel |
| Attorney Docket Number | MIT 6210 |

## ENCLOSURES *(Check all that apply)*

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| Date | March 2, 2004 |

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☐ Applicant claims small entity status. See 37 CFR 1.27

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| Application Number | 08/398,555 |
| Filing Date | March 3, 1995 |
| First Named Inventor | Linda G. Cima, et al. |
| Examiner Name | J. E. Russel |
| Art Unit | 1654 |
| Attorney Docket No. | MIT 6210 |

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| 1002 | 340 | 2002 | 170 | Design filing fee | |
| 1003 | 530 | 2003 | 265 | Plant filing fee | |
| 1004 | 770 | 2004 | 385 | Reissue filing fee | |
| 1005 | 160 | 2005 | 80 | Provisional filing fee | |

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| | | Extra Claims | | Fee from below | | Fee Paid |
|---|---|---|---|---|---|---|
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| Independent Claims | 2 | - 3** = | 0 | X | 0 | = 0 |
| Multiple Dependent | | | | | | = |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 1202 | 18 | 2202 | 9 | Claims in excess of 20 |
| 1201 | 86 | 2201 | 43 | Independent claims in excess of 3 |
| 1203 | 290 | 2203 | 145 | Multiple dependent claim, if not paid |
| 1204 | 86 | 2204 | 43 | ** Reissue independent claims over original patent |
| 1205 | 18 | 2205 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($) -0-

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| 1053 | 130 | 1053 | 130 | Non-English specification | |
| 1812 | 2,520 | 1812 | 2,520 | For filing a request for *ex parte* reexamination | |
| 1804 | 920* | 1804 | 920* | Requesting publication of SIR prior to Examiner action | |
| 1805 | 1,840* | 1805 | 1,840* | Requesting publication of SIR after Examiner action | |
| 1251 | 110 | 2251 | 55 | Extension for reply within first month | |
| 1252 | 420 | 2252 | 210 | Extension for reply within second month | |
| 1253 | 950 | 2253 | 475 | Extension for reply within third month | |
| 1254 | 1,480 | 2254 | 740 | Extension for reply within fourth month | |
| 1255 | 2,010 | 2255 | 1,005 | Extension for reply within fifth month | |
| 1401 | 330 | 2401 | 165 | Notice of Appeal | |
| 1402 | 330 | 2402 | 165 | Filing a brief in support of an appeal | 330.00 |
| 1403 | 290 | 2403 | 145 | Request for oral hearing | |
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| 1503 | 640 | 2503 | 320 | Plant issue fee | |
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Appellants: Linda G. Cima, Edward W. Merrill, and Philip R. Kuhl

Serial No.: 08/398,555 Art Unit: 1654

Filed: March 3, 1995 Examiner: Jeffrey E. Russel

For: *CELL GROWTH SUBSTRATES WITH TETHERED CELL GROWTH EFFECTOR MOLECULES*

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**APPEAL BRIEF**

Sir:

This is an appeal from the rejection of claims 14-17 and 32-34 in the Office Action mailed October 3, 2003, in the above-identified patent application. A Notice of Appeal was mailed on January 2, 2004. The Commissioner is hereby authorized to charge $330.00, the fee required for the filing of this Appeal Brief as a large entity, to Deposit Account No. 50-1868.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

## (1) REAL PARTY IN INTEREST

The real parties in interest of this application are the assignee, Massachusetts Institute of Technology, Cambridge, Massachussetts and Corning, Inc., Corning, New York, which has rights in the subject matter of this application.

## (2) RELATED APPEALS AND INTERFERENCES

This application was previously before the board of appeals as appeal number 1999-0965, remanded to the examiner in the decision mailed on July 27, 2001. There are no other related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affect, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS ON APPEAL

Claims 14-17 and 32-34 are pending. Claims 1-13 and 18-31 were canceled in the Amendment mailed August 21, 2002. Claims 14-17 and 32-34 are on appeal. The text of each claim on appeal, as pending, is set forth in the Appendix to this Appeal Brief.

## (4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed January 5, 2004. In the Advisory Action mailed January 28, 2004, the Examiner indicated that this amendment would not be entered due to typographical errors, but would be entered if re-submitted with the proper corrections. The amendment was re-submitted on February 5, 2004. An appendix sets forth the claims in this amendment.

## (5) SUMMARY OF THE INVENTION

Independent claim 33 is directed to a method for the growth of eukaryotic cells wherein the cells are grown a composition that includes a biocompatible solid substrate and tethered growth effectors (page 5, lines 6-16). The *tethered* growth effector molecules are present at an effective concentration to enhance the rate of target cell growth over the rate of target cell growth with *soluble* growth effector molecules (page 15, line 27- page 16, lines 1-2) and growth effector molecules merely *adsorbed* to a substrate, (page 24, lines 16-22) without internalization of the molecules (page 5, lines 23-30).

The tethers are made from biocompatible, synthetic, water soluble polymers (page 6, line 23- page 7, line 2) and are attached to the substrate and a growth effector molecule (page 6, line 13-14). The substrate may be in the form of netting, fibers, sponge or shaped polymers, which may have the form of dishes, bottles, solid particles, hollow particles, or a desired tissue shape (page 9, lines 25-29). The substrate may be glass, metal, or a biocompatible polymer (page 9, lines 9-24), such as a synthetic or natural polymer, like a protein, polysaccharide, extracellular matrix protein, polyester, polycapralactone, polyhydroxybutyrate, polyanhydride, polyphosphazene, polyorthoester, polyurethane, or combination thereof (page 9, lines 9-24).

Examples of the growth effector molecules include epidermal growth factor, platelet-derived growth factor, transforming growth factor, hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, extracellular matrix molecules, or combinations thereof (page 10, line 20- page 11, line 30).

Dependent claims 14-17 further limit the scope of claim 33. Claim 14 recites cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, maleimide, and carbodiimide as possible attachment agents (page 12, lines 6-8). Claim 15 is directed to administration of the composition by injection, infusion, or implantation (page 18, lines 16-17). Claim 16 is directed to administration of the composition by implantation and wherein the substrate is shaped to match a desired tissue shape (page 18, lines 5-8). Claim 17 is directed to the substrate being biodegradable (page 9, lines 14-24).

Independent claim 34 is directed to a method for testing the effect of a compound on tissue, which includes exposing the compound to cells growing on the composition as defined in claim 33 (page 18, lines 24-27).

**(6) ISSUES ON APPEAL**

(1) whether claims 14-16 and 33 should be rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,370,681 to Herweck et al. ("Herweck"), in combination with U.S. Patent No. 5,171,264 to Merrill ("Merrill");

(2) whether claim 17 should be rejected under 35 U.S.C. §103 as obvious over Herweck in combination with Merrill, further in view of U.S. Patent No. 5,522,895 to Mikos et al. ("Mikos");

(3) whether claims 14-17 and 33 should be rejected under the judicially created doctrine of obviousness-type double patenting as obvious over claims 1-4 of U.S. Patent No. 5,906,828 to Cima et al. ("Cima '828") and further in view of U.S. Patent No. 4,954,637 to

Nitecki et al ("Nitecki"), U.S. Patent No. 5,508,164 to Kausch et al.("Kausch") and the appellants' alleged admissions; and

(4) whether claims 32 and 33 should be rejected under the judicially created doctrine of obviousness-type double patenting as obvious over claim 20 of U.S. Patent No. 6,045,818 to Cima et al. ("Cima '818") and further in view of Nitecki, Kausch and the appellants' alleged admissions.

## (7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (1) claims 14-17 and 33 and (2) claims 32 and 34. Group 1 claims are directed to a method for growing eukaryotic cells by bringing the cells into contact with a composition comprising a biocompatible solid substrate, biocompatible polymeric tethers, and growth effector molecules, wherein the growth effector molecules are linked to the substrate by a tether, which prevents internalization of the growth effector molecules by cells attached to the substrate. Group 2 claims are directed to a method of using the compositions as described in the Group 1 claims for testing a compound for its effect on tissue by contacting the compound with the composition and growing cells. Both of the groups require a separate analysis as to patentability since they contain different elements.

## (8) ARGUMENTS

### (a) The Claimed Invention

The claims are directed to methods for enhancing cell growth or for testing the effect of a compound on tissue that include a composition comprising a biocompatible substrate, polymeric tethers, and growth effector molecules, wherein the molecules are covalently linked to one end of a tether and another end of the tether is covalently linked to the substrate. The growth effector molecules can freely interact with the cell but are not internalized by the cell.

Most currently used cell and tissue growth compositions include soluble growth effector molecules, such as growth factors, either as an additive or as a component of complex growth media. The use of soluble growth effector molecules has certain drawbacks, such as loss in responsiveness of the cells to the molecules. Cells have a complex, nonlinear response to the concentration of growth factor in their environment and extended exposure to high growth factor concentrations may cause cells to lose responsiveness to the factor. For example, epidermal growth factor (EGF), a potent mitogen for a wide variety of cell types and arguably the best-characterized of the growth factors, is typically internalized by the cell when delivered in soluble form, and the cell often responds by down-regulating the number of EGF receptors. This down-regulation causes cells to lose responsiveness to EGF. The growth effector molecules of the compositions in the claims are tethered and cannot be internalized by the cells. Therefore, receptor down-regulation is avoided.

The effectiveness of the growth effector molecules on the rate of cell growth is maintained, and in fact enhanced, because the growth effector molecules are linked to the ends of

tethers that provide mobility to the molecules sufficient for the molecules to contact receptors in the cell membrane, but without allowing internalization of the molecules. The polymers of the claimed compositions and methods are soluble in aqueous solution and will extend to their full length, providing a wide range of movement (flexibility) to the factors attached thereto. This is a very important aspect of Appellants' tethers. As discussed in the application at page 6, lines 6-8 and 11-26 and page 7, lines 21-30, the tether must be flexible to allow the growth effector molecule to contact the receptor on the cell surface and also to allow the growth effector molecule-receptor complex to move within the cell membrane. See, for example, the Specification at page 6, line 19, "Substantial mobility of a tethered growth factor is critical . . . ."

Not only do the tethers used in Appellants' claimed compositions and methods extend and provide mobility to the attached molecules but the tethers do not interact with the cell. This attribute also allows free movement of the molecules so that the molecules can contact the cell receptors and allow aggregation of growth effector molecule/receptor complexes on the cell membrane. See the Specification at page 5, line 24 through page 6, line 10.

The molecules are attached in a concentration effective to enhance the rate of growth of the target cells over the rate of cell growth with soluble or adsorbed growth effector molecules. The amount and types of tethers must be properly balanced with the amounts of growth effector molecules to achieve enhanced growth rate. Because the tethers are water soluble, they are flexible and allow substantial mobility to the attached molecules. However, the tethers are also cell repellent and therefore could discourage cell growth. The use of branched tethers, in particular, avoids this potential problem by minimizing the amount of tether material, while

achieving effective growth effector molecule concentration. Appellants have avoided sterically hindering contact of growth effector molecules with the receptors in the cell membrane. Appellants show how to enhance the rate of cell growth as compared to the rate of cell growth with soluble or adsorbed molecules by balancing use of polymeric water soluble tethers which do not bind to cells and the use of the proper amounts of tethered growth effector molecules.

Another problem with the use of soluble growth effector molecules, which is avoided by the claimed compositions and methods, is that growth effector molecules, when placed in a complex cellular environment, often end up stimulating the growth of competing cells which then overgrow the target cells. Researchers have attempted to solve this problem by targeting delivery of factors at a specific site, but this approach is not always successful because soluble growth factors can readily diffuse into the blood stream and away from the target site, exerting their effects elsewhere. This diffusion of growth factors is also a problem because it increases the amount of growth factor that must be used in order to have the desired local effect. Internalization of growth factors and loss of responsiveness to growth factors is a particular problem for *in vivo* applications considering the amount of time cell growth must be stimulated to allow wound healing.

Another strategy to improve the longevity of growth effector molecule effects *in vivo* has been to incorporate the molecules in a slow release material, such as by adsorbing the molecules to a substrate. Such a scheme still requires large amounts of growth effector molecules and does not address the problem of competing cell growth due to diffusion of the molecules. The large

amount of growth effector molecules needed for these cell and tissue growth methods is a particular problem because these molecules are difficult and expensive to prepare.

The tethers are preferably branched and water soluble so that each tether is able to covalently bind more than one growth effector molecule. By using a multi-functional flexible tether, Appellants can go to very low factor concentrations and still achieve receptor aggregation by virtue of having more than one factor on each tether. So, even though the tethers can be very far apart (i.e. the distance from the center of one tether to the center of the adjacent tether is more than twice the fully extended chain length of the tether), receptor-receptor interactions can still occur in the membrane after growth effector molecule binding because the molecules are locally clustered. If linear tethers, i.e. tethers with only one attachment site for a growth effector molecule and one attachment site to the substrate, are used, going to lower concentrations also increases the distance between factors and potentially inhibits the ability of receptor-molecule complexes to interact in the cell membrane. Thus, at lower concentrations, signaling may not occur at all using linear tethers, because the molecules are homogeneously spaced on the surface.

Appellants' tethers can bind more than one molecule of the same growth effector or can bind different growth effector molecules. Thus, the density of a growth effector molecule on a substrate can be increased without substantially increasing the number of cell-repellant tethers. Alternatively, for example, both insulin and EGF could be tethered to the same substrate, allowing presentation of two or more molecules to the cell.

**(b) Rejections Under 35 U.S.C. § 103**

The Legal Standard

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a suggestion to make the claimed invention and a reasonable expectation of success. It is also clear that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. Particularly relevant to the matters under consideration here are the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court noted that:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.... Both the suggestion and expectation of success must be founded in the prior art, not in the Appellant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, *the full field of the invention must be considered*: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.... Evidence that supports, rather than negates, patentability must be fairly considered.

5 USPQ 2d at 1531-1532 (Citations omitted, emphasis added).

In *In re Dow Chemical*, a combination of three components forming an impact resistant rubber-based resin was not found to be obvious based upon art disclosing the individual components. The court noted that the record had shown that the claimed combination had previously been made, *but did not produce the product desired.* "That there were other attempts, and various combinations and procedures tried in the past, does not render obvious the later successful one.... Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness," *Id.* at 1531 (citations omitted). The Court found that none of the prior art cited by the Appellant and the PTO suggested that any process could be used successfully in this three-component system to produce the product having the desired properties. Further, the Court stated that evidence from an expert expressing skepticism as to the success of the claimed combination before these inventors proved him wrong should be considered. *Id.* at 1532.

i. Rejection of Claims 14-16 and 33 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,370,681 to Herweck et. al. ("Herweck") in view of U.S. Patent No. 5,171,264 to Merrill ("Merrill").

**Claims 14-16 and 33 are not Obvious over Herweck in Combination with Merrill**

Herweck discloses implantable devices for sustained release of a bioactive material, such as a therapeutic agent, a cell type, or a diagnostic agent, into a fluid flow pathway of a patient (see column 3, lines 14-16 and 30-37). Herweck discloses first coating or modifying the surface with glycoproteins such as fibronectin prior to seeding the device with cells (see column 4, lines 62-68). Herweck discloses that such a coating may result in improved adhesion of cells (see column 6, lines 23-29). As recognized by the Examiner, Herweck does not disclose or suggest

the use of a tether attaching a growth effector molecule to a substrate but merely coats, or adsorbs, the factor upon the substrate. More importantly, Herweck does not describe or provide the motivation to lead one of ordinary skill in the art to grow cells by maintaining the cells in contact with the composition defined therein, which comprises a tether attaching a growth effector molecule to a substrate without causing internalization of the effector molecule by the cells. Furthermore, Herweck does not teach that the rate of target cell growth would be enhanced by using tethered growth effector molecules as compared to simply coating or adsorbing the growth effector molecules to the substrate.

Briefly, Herweck does not recognize the critical concentration of growth effector molecules, the need for a tether that allows the growth effector molecules to enhance the rate of growth without internalization of the growth effector molecules, or the role the tethers and linkers play in such a substrate.

Merrill discloses star molecules of polyethyleneoxide (PEO) that are biocompatible and demonstrate non-thrombogenic properties. These star molecules could be useful in Appellants' methods, as discussed in the specification at page 7, lines 3-20. Merrill teaches that the star PEO molecules can be attached to an appropriate support surface to reduce thrombosis, to assist in protein purifications, and other proposed activities. However, Merrill does not suggest the importance of length or density of the tethered growth factors on the substrate to which the star molecules are to be attached.

As shown in Figure 4, Merrill describes using PEO molecules as tethers for attaching IgG, which is not a growth effector molecule. Merrill does not recognize the criticality of the

concentration of growth factors to enhance growth, the requirement for tethers which allow the growth factors to bind to cells but which prevent internalization, or the role linkers play.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. Accordingly, Herweck does not suggest that it would be advantageous to tether growth factors to the substrate, and Merrill does not suggest using the star molecules for tethering growth effector molecules to a substrate. The primary use for the star molecules that is described in Merrill is for separating and purifying therapeutic proteins. Other proposed uses are described at column 6, lines 6-27.

Moreover, even if the teachings of the references are combined, the combination does not suggest the claimed compositions or methods because it does not suggest attaching growth effector molecules in a concentration and with tethers to a substrate so that the rate of cell growth is enhanced over the rate of cell growth with soluble growth effector molecules or growth effector molecules adsorbed to a substrate. Furthermore, one skilled in the art would not combine these references and automatically envisage the specific use of covalent tether linkages to prevent growth effector internalization by the cells.

In fact, Merrill teaches away from the claimed compositions and methods because it discloses that the PEO star molecules are non-thrombogenic, i.e., do not absorb proteins of the intrinsic clotting system or of the platelet membrane (see Merrill, column 1, lines 6-9). One of ordinary skill in the art would thus know that the use of PEO as a tether would tend to repel cells,

and would thus believe that PEO would not allow contact of the attached growth effector molecules with the cells.

Appellants use PEO, or similar polymeric tethers, which are water soluble so that they unfold in solution and provide flexibility to the molecules tethered thereon, and able to contact cells so as to provide enhanced cell growth.

In summary, Herweck and Merrill, even if someone were led to combine them, would not lead one of ordinary skill in the art to make and use a composition as defined in the claims for stimulating cell growth; nor would Herweck and Merrill, combined, lead one of ordinary skill in the art to have a reasonable expectation that the claimed method could be used as defined by claim 34. Therefore, claims 14-16, and 33 are not *prima facie* obvious over Herweck in view of Merrill ((*see*, *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *see also* MPEP § 2141).

ii. Rejection of Claim 17 under 35 U.S.C. § 103(a) over Herweck in view of Merrill, and further in view of U.S. Patent No. 5,522,895 to Mikos *et al.* ("Mikos").

**Claim 17 is not Obvious over Herweck in Combination with Merrill and Mikos**

Claim 17 is dependent upon claims14-16 and 33, which, as discussed above, are not obvious from Herweck and Merrill. Mikos does not add the elements missing from the Herweck/ Merrill combination.

Mikos describes a biodegradable polymeric matrix which can be seeded with cells and implanted. In particular, Mikos describes a biodegradable, bioresorbable, three-dimensional template for repair and replacement of diseased or injured bone (col. 2, lines 10-57).

Mikos discloses biodegradable polymers, but provides no teaching that one should tether growth effector molecules to a biodegradable substrate, only that one should directly absorb cells to a biodegradable substrate. Therefore, Herweck in view of Merrill in combination with Mikos would not make claim 17 obvious. Only with hindsight would one be led to combine Mikos, Merrill and Herweck. There is no teaching that would lead one to the combination. Even in combination, the three references do not disclose or make obvious chemically coupling growth effector molecules to a biodegradable substrate in a density and with appropriate linkers to result in the enhanced growth of attached cells over the rate of cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules. (*see*, *Hodosh v. Block Drug Co., Inc.*, 786 F.2d at 1143 n.5, 229 USPQ at 187 n.5; *see also* MPEP § 2141).

**(c) Rejections Under the Doctrine of Obviousness-Type Double Patenting**

This application was filed March 3, 1995, and therefore any patent issuing on the application will have a patent term of seventeen years from the date of issue. This case has twice been on appeal, and that is the major reason it has now been pending for nine years.

Appellants prosecuted a continuation case while this case was on appeal and were able to convince the examiner that substantially narrower claims should be allowed. The Board then

remanded this case to the examiner, it was again prosecuted, and appellants are now back before the Board.

Double patenting is an equitable doctrine. The purpose is to prevent applicants from being unjustly rewarded for pursuing closely related subject matter in claims expiring over a longer period of time than if the claims would have issued all in one patent.

Equity in this case must be on the side of the appellants. Appellants have diligently prosecuted this case and have tried over a period of nine years to place these claims in condition for allowance. They should not be penalized because they were able to convince the examiner to allow significantly more narrow claims. Requiring a terminal disclaimer at this point would result in a loss of ***at least seven years of patent term.*** This would be grossly unfair and inequitable to appellants.

The Examiner Failed to Apply the Correct Test for Obviousness-Type Double Patenting

In order to support his rejection of the claims, the Examiner used a "one-way" patentability test. Federal Circuit decisions have confirmed that a "two-way" rather than a "one-way" patentability test applies when an inventor or assignee files a patent application claiming an improvement or combination invention *after* a patent application claiming the basic or subcombination invention, but the *second-filed application issues first* through no inventor or assignee fault. See re Braat, 937 F.2d 589, 19 USP Q2d 1289 (Fed. Cir. 1991). Therefore, the proper test in this case is not a one-way test for obviousness as proposed by the Examiner, but a two way test since the two patents claiming an improvement were filed after this application but issued first.

i. Rejection of Claims 14-17, and 33 over claims 1-4 of U.S. Patent No. 5,906,828 to Cima et al. ("Cima '828") and further in view of U.S. Patent No. 4,954,637 to Nitecki et al. ("Nitecki"), U.S. Patent No. 5,508,164 to Kausch et al., ("Kausch") and the appellants' alleged admissions.

**Claims 14-17 and 33 are not Obvious over Cima '828 in Combination with Nitecki and Kausch.**

This application was filed prior to Cima '828, but was subject to an administrative delay on the part of the PTO during the appeal process. Where a two-way obviousness determination is required, it is necessary to apply the Graham obviousness analysis twice, once with the application claims as the claims in issue, and once with the patent claims as the claims in issue. In this situation, an obvious-type double patenting rejection is appropriate only where each analysis compels a conclusion that the invention defined in the claims in issue is an obvious variation of the invention defined in a claim in the other application/patent.

If a two-way test for obviousness is applied, it is clear that the claims of Cima '828 and the claims of the current application are not obvious variations of each other.

Claims 1-4 of Cima '828 define a method of growing eukaryotic cells:

1. A method for growing eukaryotic cells comprising

(a) bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible branched water soluble polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and

the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

(b) maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow;

wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

Claims 2-4 further define the route of administration of the composition and the shape and biodegradability of the substrate in the method of claim 1.

First, an analysis must be performed with the application claims as the claims in issue. Claims 14-17 and 33 do not require administration of cells to a patient. There is nothing within claims 14-17 and 33 which would lead one skilled in the art to believe the subject matter is a therapeutic. Only the claims may be considered in a double patenting rejection - no reference back to the specification or other materials to support the rejection. There is nothing that would lead one skilled in the art to look at claims 14-17 and 33, and suggest the additional step of administering the composition to a patient, as defined by the claims of Cima '828.

Therefore, claims 14-17 and 33 are not obvious from the claims of Cima '828 when the claimed invention is considered as a whole.

Next, one must perform an analysis with the patent claims as the claims in issue. Claim 1 of Cima '828 stipulates that each tether is branched and able to covalently link more than one growth effector molecule. These claim limitations are not found in claim 33 of the present application, nor are they found in claims 14-17. Thus, claims 1-4 of Cima '828 are not *prima facie* obvious over claims 14-17, and 33.

Finally, Nitecki and Kausch do not disclose the elements missing from claims 1-4 of Cima '828, nor is there any motivation to combine these references. Nitecki and Kausch teach linkers for coupling biological agents, but nowhere in the disclosures of these two patents does it suggest that the respective inventions would be useful for growing cells on a biocompatible solid substrate.

ii. Rejection of Claims 32 and 34 over claim 20 of U.S. Patent No. 6,045,818 to Cima et al. ("Cima '818") and further in view of Nitecki, Kausch and the appellants' alleged admissions.

**Claims 32 and 34 are not Obvious over Cima '818 in Combination with Nitecki and Kausch.**

A "two-way" test should also be applied to claims 32 and 34 since the current application was filed prior to Cima '818, but was subject to an administrative delay on the part of the PTO during the appeal process. Claims 32 and 34 are drawn to a method for screening for a compound for an effect on tissue comprising bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible, polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and one end is covalently linked to a growth effector molecule so that the growth effector molecule cannot be internalized by cells attached to the substrate;

wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules;

wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents; and

wherein the growing cells are bound to the growth effector molecules; incubating the compound and the composition under conditions promoting cell growth; and observing the cells for any effect not observed in cells not brought into contact with the composition.

Claim 20 of Cima '818 defines a method of testing a compound for an effect on tissue, as follows:

20. A method of testing a compound for an effect on tissue comprising

(a) bringing into contact the compound to be tested and a composition comprising a biocompatible solid substrate,

biocompatible branched water soluble polymeric tethers comprising a polymeric material selected from the group consisting of polyethylene oxide, polyvinyl alcohol, polyhydroxyalkyl (meth)acrylate, polyacrylamide, and starches,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules, and

wherein the growing cells are bound to the growth effector molecules;

(b) incubating the compound and the composition under conditions promoting cell growth; and

(c) observing the cells for any effect not observed in cells not brought into contact with the composition,

wherein the substrate is selected from the group consisting of glasses, metals, polystyrenes, polyethylene vinyl acetates, polypropylenes, polymethacrylates, polyacrylates, polyethylenes, polyethylene oxides, polysilicates, polycarbonates, polytetrafluoroethylene, fluorocarbons, nylon, silicon rubber, polyanhydrides, polyglycolic acids, polyhydroxyacids,

polyesters, polycapralactone, polyhydroxybutyrate, polyphosphazenes, polyorthoesters, polyurethanes, and combinations thereof .

Like claim 1 of Cima '828, claim 20 of Cima '818 stipulates that each tether is branched and able to covalently link more than one growth factor molecule. However, these claim limitations are not found in claim 34 of the present application, nor are they found in claim 32. Therefore, claim 20 is not *prima facie* obvious over claims 32 and 34.

There is nothing in claims 32 and 34 that would lead one skilled in the art to substitute branched tethers for tethers as currently defined. Absent some teaching, claims 32 and 34 cannot be obvious over the claims in Cima '818.

Finally, Nitecki and Kausch do not disclose the elements missing from claim 20 of Cima '818, nor is there any motivation to combine these references. As stated above, Nitecki and Kausch teach linkers for coupling biological agents, but nowhere in the disclosures of these two patents does it suggest that the respective inventions would be useful for growing cells on a biocompatible solid substrate.

## (9) SUMMARY AND CONCLUSION

With respect to the rejections under 35 U.S.C. § 103, the cited prior art references do not teach or suggest methods for enhancing cell growth involving the use of a polymeric tether attached to a substrate that is able to bind growth effector molecule so that (1) the molecules cannot be internalized by the cell and (2) the growth rate of target cells is enhanced as compared to the rate of cell growth of cells exposed to soluble and adsorbed growth effector molecules.

Indeed, it is surprising that Appellants obtained the results observed, because there was as great a likelihood that the coupled growth factors would sterically hinder binding of the growth factors to the cell, actually decreasing the effectiveness of the growth factors on the cell growth rate, as there was that the same, much less enhanced, rate of growth would be observed when growth factors were administered in soluble form or adsorbed to the substrate. The Examiner has not pointed to any literature that would indicate that one skilled in the art would predict that the claimed compositions would affect cell growth rate in any manner differently than the same growth effector molecule immobilized on the substrate, much less enhance it.

Finally, the obviousness-type double patenting rejections are improper because applying the two-way obviousness test demonstrates that neither the claims in issue nor the claims in Cima '828 or Cima '818 are obvious variations of each other. In addition, the combination of Nitecki and Kausch do not teach or suggest the limitations of the claims in issue nor is there any motivation to combine these references with the issued patents. Finally, upholding the double patenting rejection would be grossly unfair to appellants.

For the foregoing reasons, Appellants submit that claims 14-17 and 32-34 are patentable.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: March 2, 2004

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

**CERTIFICATE OF FACSIMILE TRANSMISSION**

I hereby certify that the enclosed Appeal Brief and all documents shown as being attached is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.

Patrea L. Pabst

Date: March 2, 2004

## Appendix: Claims On Appeal

Claims 1-13 (canceled)

14. (previously presented) The method of claim 33 wherein the attachment agent is selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, maleimide, and carbodiimide.

15. (original) The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. (original) The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. (original) The method of claim 16 wherein the substrate is biodegradable.

Claims 18-31 (canceled)

32. (previously presented) The method of claim 34 wherein the attachment agent is selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, maleimide, and carbodiimide.

33. (previously presented) A method for growing eukaryotic cells comprising

bringing into contact the cells with a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and one end is covalently linked to a growth effector molecule so that the growth effector molecule cannot be internalized by cells attached to the substrate;

wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents, maintaining the cells in contact with the composition under conditions and for a time sufficient to cause the cells to grow.

34. (previously presented) A method of testing a compound for an effect on tissue comprising bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible, polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and one end is covalently linked to a growth effector molecule so that the growth effector molecule cannot be internalized by cells attached to the substrate;

wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble

growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules;

wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents; and

wherein the growing cells are bound to the growth effector molecules; incubating the compound and the composition under conditions promoting cell growth; and observing the cells for any effect not observed in cells not brought into contact with the composition.

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## (9) SUMMARY AND CONCLUSION

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